TABLE 2. Relative risks associating breast cancer with passive and active smoking*

Study	Cases		Controls or population		Adjusted relative risk†	95% confidence interval	Statistical weight
	No.	% exposed	No.	% exposed			
Passive smoking							
Sandler‡ (3)	32	59	177	43	1.62	0.76–3.44	6.7
Hirayama‡ (3)	115	80	91,540	76	1.32	0.83–2.09	18.0
Smith et al. (1)	94	49	100	37	1.58§	0.81–3.10§	8.5
Morabia et al. (2)	126	78	620	61	2.3	1.5–3.7	19.0
Combined	367				1.83	1.40–2.40	52.2
Active smoking							
Sandler‡ (4)	40	68	248	59	1.21	0.58–2.51	7.2
Hirayama¶	60	62	39,261	44	2.03	1.22–3.38	14.8
Smith et al. (1)#	87	45	96	34	2.00	0.98–4.12	7.5
Morabia et al. (2)**	146	81	652	63	3.0	1.9–4.8	17.9
Combined	333				2.17	1.63–2.88	47.4

* Passive smoking is for never smokers only. Subjects who never smoked and who were not exposed to environmental tobacco smoke constitute the reference category for both active and passive smoking. For active smoking, % exposed is the proportion of ever smokers to ever smokers plus non-environmental tobacco smoke-exposed never smokers.

† Odds ratios from the case-control studies are assumed to be reasonable approximations to relative risk.

‡ Data obtained from Drs. Dale P. Sandler and T. Hirayama by means of personal communications and published in two previous letters by Wells (3, 4).

§ For partner exposure only. Odds ratio for total adult exposure was 3.13 (95% CI 0.73–13.31).

¶ Author's calculation based on population data in Hirayama (6) and active relative risk from T. Hirayama, Institute of Preventive Oncology, Tokyo, Japan, personal communication, 1988.

S.J. Smith, University of Nottingham Medical School, Nottingham, United Kingdom, personal communication, 1996.

** Combined odds ratios for all ever smokers in table 2 of Morabia et al. (2), from A. Morabia, Hôpital Cantonal Universitaire, Geneva, Switzerland, personal communication, 1997.

results indicated here. Women are known to fear breast cancer. If breast cancer is indeed caused by cigarette smoke, women need to know that, not only to reduce their breast cancer risk by avoiding smoke but also to improve public health generally through a reduced prevalence of smoking.

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RE: "SMOKING AND BREAST CANCER: RECONCILING THE EPIDEMIOLOGIC EVIDENCE BY ACCOUNTING FOR PASSIVE SMOKING AND/OR GENETIC SUSCEPTIBILITY"

Wells (1) reports that four studies conducted in different populations and with different designs consistently show that women exposed to passive smoking as well as those exposed to active smoking are at increased risk of breast cancer relative to women unexposed to either. These results are disturbing for at least two reasons. First, as mentioned by Whidden (2), reported associations of breast cancer with active versus nonactive smoking have, in general, been either weakly positive or absent. Second, the relation does not appear to be related to dose of exposure to tobacco smoke, since the combined relative risk for passive smoking (relative risk = 1.8) is of the same magnitude as that for active smoking (relative risk = 2.1).

These puzzling findings could, of course, be attributed simply to a yet-undetermined bias, because they are too aberrant compared with findings in the rest of the literature. However, an additional study (not cited by Wells (1) or Whidden (2)) has furthered understanding of the relation between smoking and breast cancer risk. Ambrosone et al. (3) found that among slow acetylators of aromatic amines

TABLE 1. Percentages of unexposed women, passive smokers, and active smokers, and relative risks of breast cancer as approximated by odds ratios according to tobacco smoke exposure and acetylation status; hypothetical data*

Exposure to tobacco smoke	All				Rapid acetylators*				Slow acetylators*			
	Cases (%)†	Controls (%)	Odds ratio†		Cases (%)	Controls (%)	Odds ratio		Cases (%)	Controls (%)	Odds ratio	
Unexposed	19	31	1.0	1.0	35	30	1.0	1.0	10	32	1.0	1.0
Passive	43	40	1.8		35	40	0.8		48	40	3.8	
Active	38	29	2.1	1.5	30	30	0.9	1.0	42	28	4.8	1.9
All	100	100			100	100			100	100		

* Prevalences of slow acetylators among cases is 0.30 for unexposed, 0.70 for passive smokers, and 0.70 for active smokers; among controls, it is 0.50 for each of the smoking categories.
† Derived from table 2 in Wells (1).

(rapid acetylators being better able to inactivate the potentially carcinogenic tobacco compounds), the risk of breast cancer was increased in postmenopausal women who actively smoked compared with those who never actively smoked.

Could it be that the studies by Ambrosone et al. (3) and the four studies pooled by Wells (1) essentially show the same phenomenon; that is, women who develop breast cancer as a consequence of either active or passive smoking are more likely to be slow acetylators?

We have stratified the data reported by Wells (1) according to NAT2 status using, when possible, information derived from Ambrosone et al. (3) and from the literature (table 1). As observed in the populations of Ambrosone et al. and, more generally, in Caucasian populations (4), the population prevalence of the NAT2 slow-acetylation trait is about 50 percent. We can therefore expect to find this prevalence among population controls across all smoking categories. Among cases, Ambrosone et al. found that about 70 percent of active smokers who developed breast cancer were slow acetylators. We postulate that the same prevalence applies to passive smokers.

On the basis of these hypothetical prevalences, and assuming relative risks of 1.8 for passive smokers and 2.1 for active smokers, respectively, as found by Wells (1), we can compute the relative risks of breast cancer separately for slow and rapid acetylators. Table 1 shows that the results reported by Wells are compatible with the finding that passive and active smoking increase breast cancer risk in slow but not in rapid acetylators.

Table 1 also indicates that if we pool passive smokers with women unexposed to either active or passive smoke to form the reference group (vs. active smokers), the relative risk of breast cancer for active smoking is 1.5 in the total sample, 1.9 in slow acetylators, and 1.0 in rapid acetylators. That is, these relative risks are consistent with previous reports of active smoking and breast cancer from studies lacking information on acetylation status and passive smoking (5) as well as with the findings of Ambrosone et al. (3).

Thus, going back to the two reasons for concern mentioned above, it seems that under a reasonable set of assumptions, the hypothesis of a gene-smoking interaction can reconcile the apparently divergent body of epidemiologic evidence relating tobacco smoke to breast cancer. Moreover, the absence of a dose response may reflect the fact that genetically susceptible women can develop breast cancer as a result of exposure to a relatively low dosage of tobacco carcinogens. This genetic susceptibility may stem from the slow variant of NAT2, from another polymorphism, or, most probably, from a more complex, polygenic effect.

Whidden (2) suggests that previous studies should be reanalyzed, taking into account the contamination of the reference group with passive smokers. We caution that this is only one facet of the problem, the other being the validity of the exposure assessment to passive and active smoking. We recommend considering as passive smokers only those subjects who have been exposed to other people's smoke for at least 1 hour per day for at least 1 year and measuring exposure to active and passive smoking at different periods during a lifetime.

Whidden (2) also asks whether we can provide information about the passive exposure of the active smokers. We have done this analysis (Curtin et al., submitted for publication): on average, among our population controls who were active smokers, the cumulative lifetime passive exposure to tobacco smoke was equivalent to 3 hours per day for 25 years. The main sources of exposure were home and work. These data suggest that a Swiss smoker gets substantial exposure to other people's smoke in addition to the smoke inhaled from her own cigarettes.

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